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## (54) Abstract Title In-vivo photoacoustic measurement

(57) A biological parameter is measured by directing laser pulses from a light guide (10) into a body part consisting of soft tissue, such as the tip of a finger (12), to produce a photo-acoustic interaction. Sound waves (14) generated by absorption of the optical beam are detected by a transducer (16). The detector and optical beam guide are housed in a body-part shaped sensor head device (figures 2 to 16), and are preferably not co-linear with one another. Analysis of the transducer output enables calculation of the desired parameter, e.g. blood glucose concentration.

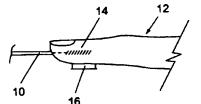


Fig. 1a

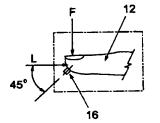


Fig. 1b

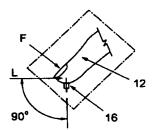


Fig. 1c

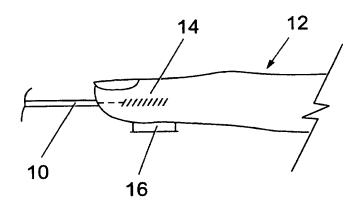


Fig. 1a

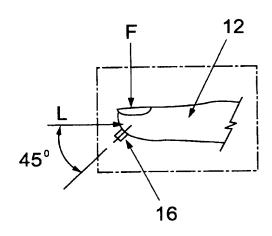


Fig. 1b

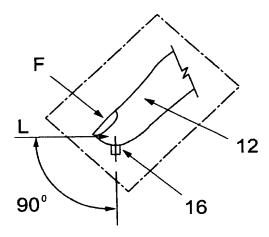


Fig. 1c

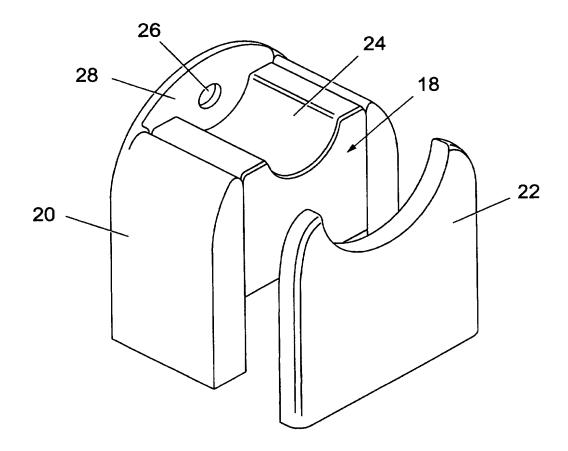
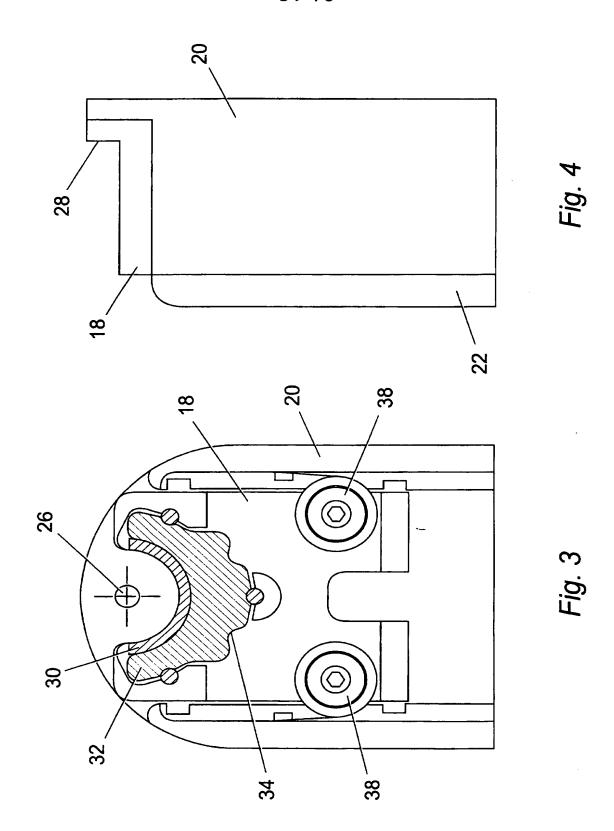


Fig. 2



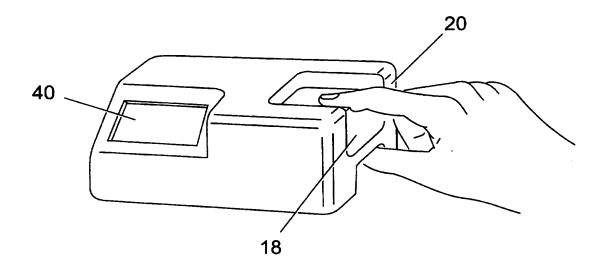
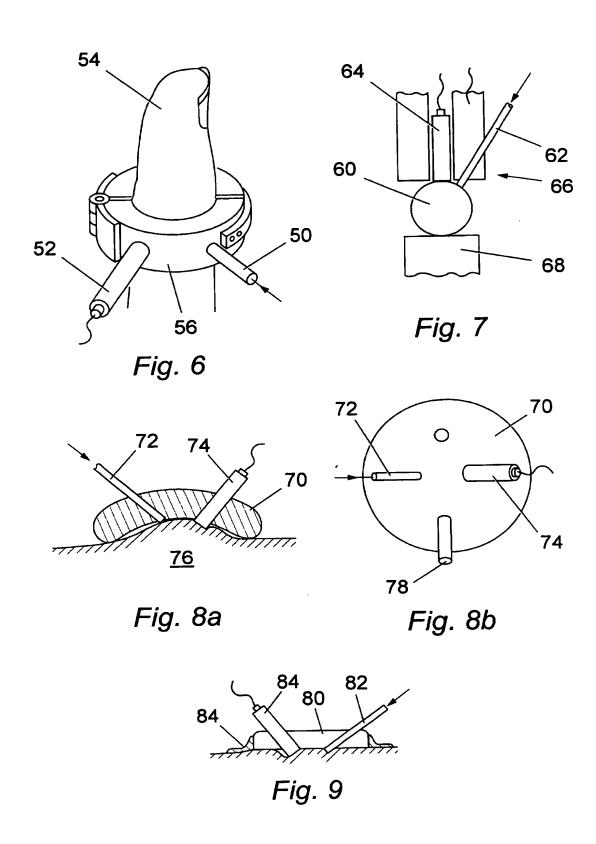
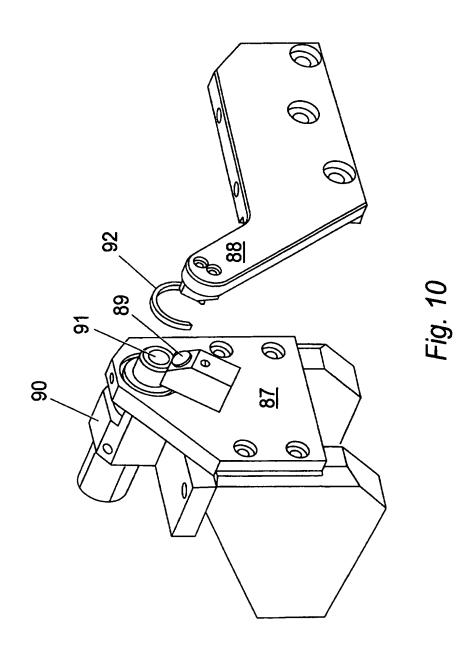
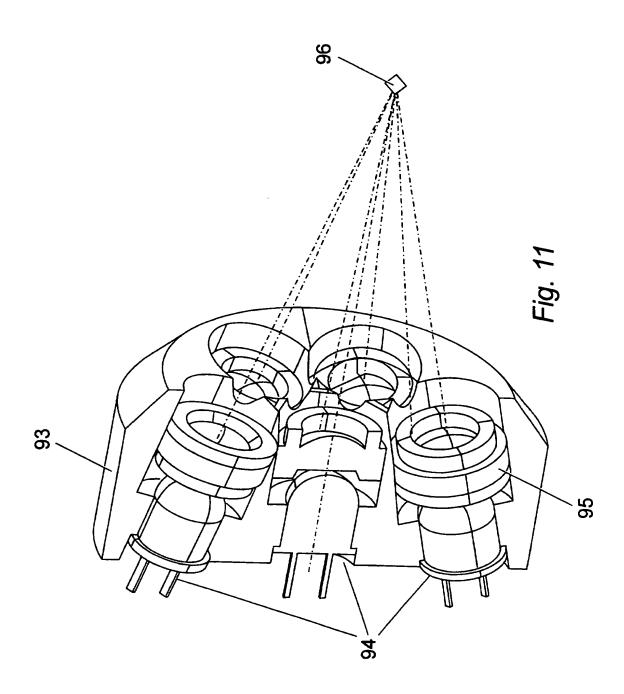
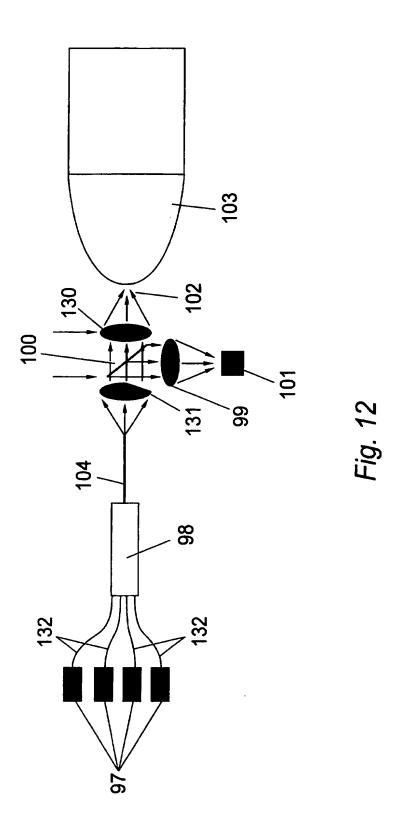


Fig. 5









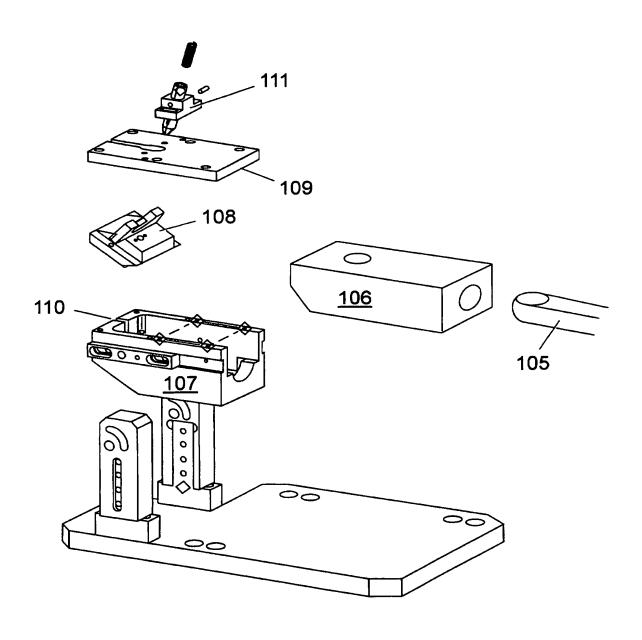


Fig. 13

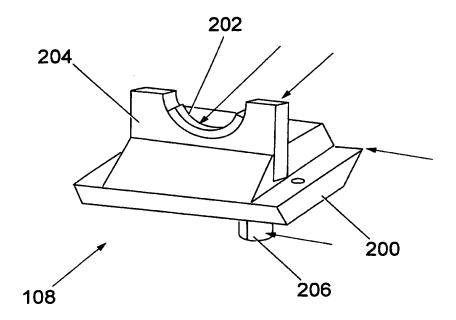


Fig. 13a

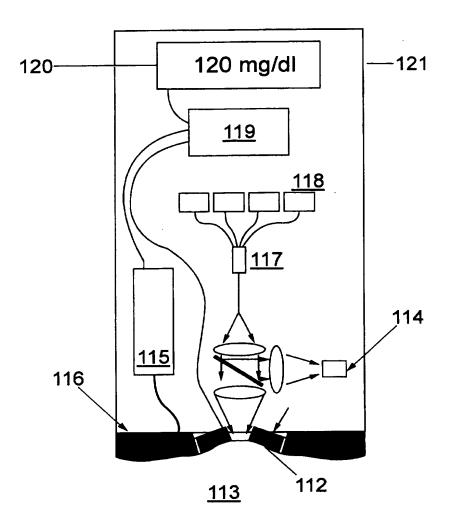
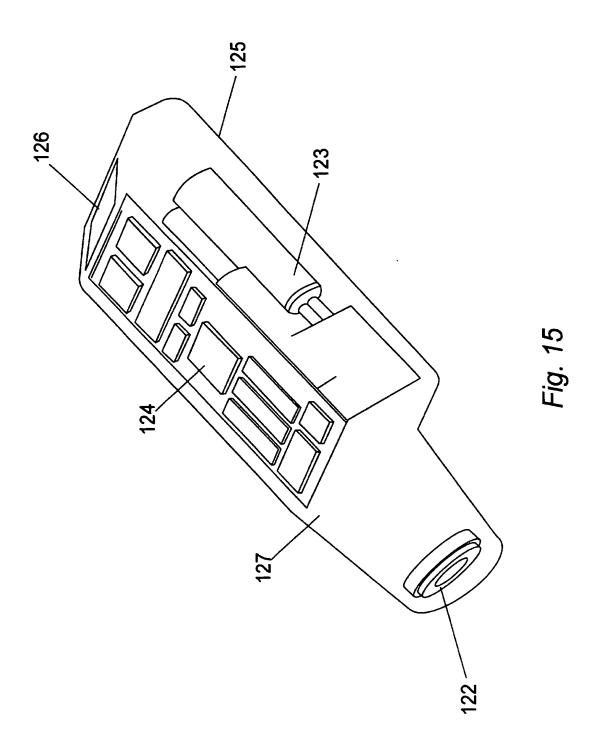
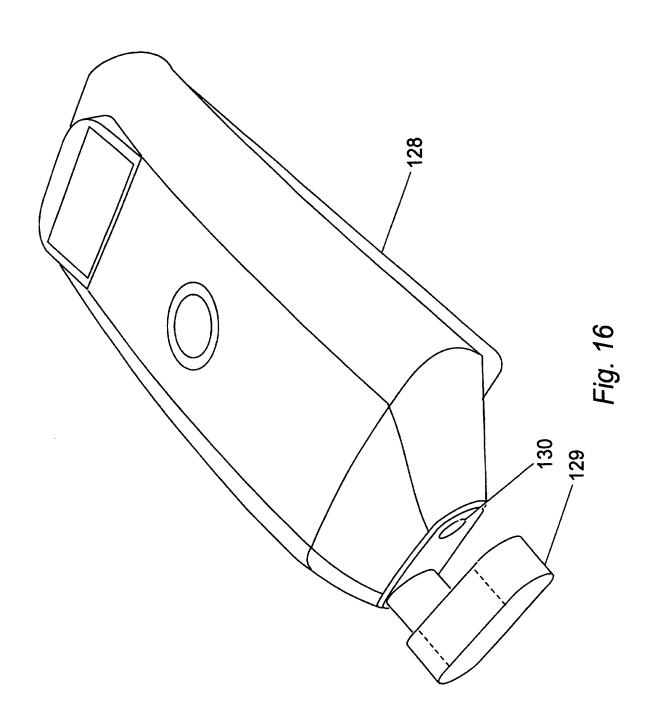
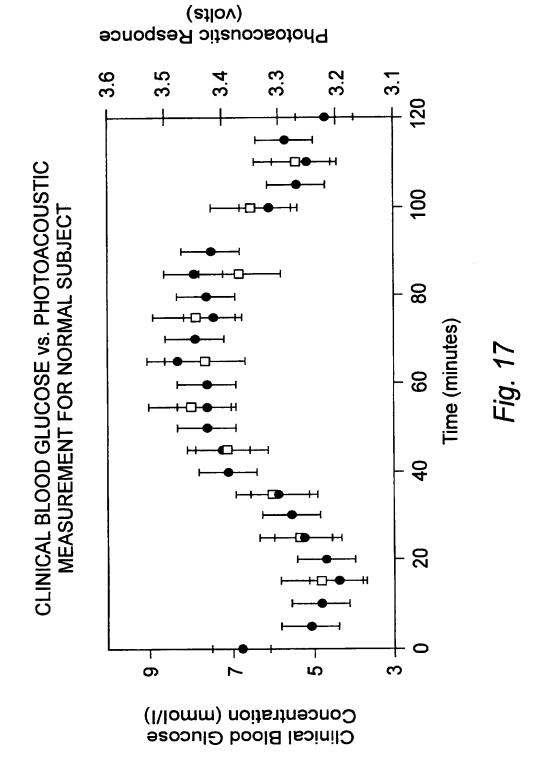


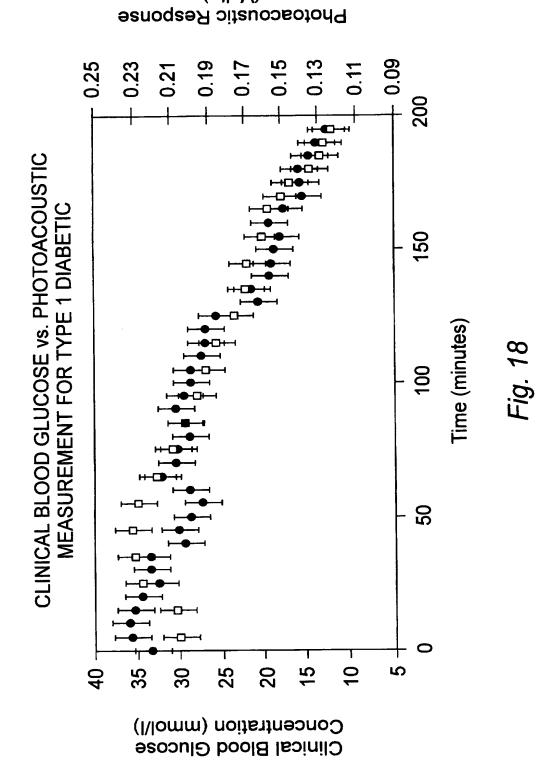
Fig. 14







(Volts)



Photoacoustic Response (volts)

-0.150.35 0.25 0.65 0.55 0.45 120 CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC MEASUREMENT FOR TYPE 2 DIABETIC 100 8 Time (minutes) 9 40 20 20-10-25-15-ဗ္ဗ 2

Clinical Blood Glucose Concentration (mmol/l) Fig. 19

1 Biological Measurement System 3 This invention relates to apparatus for use in noninvasive in vivo monitoring of physiological substances such as blood and the like. 5 7 One particular, but not exclusive, application of the present invention is in the monitoring of blood 9 glucose, for example in the management of diabetes 10 It is accepted that the management of 11 diabetes can be much improved by routine monitoring of 12 blood glucose concentration and clinicians suggest that 13 monitoring as often as four times per day is desirable. 14 15 The monitoring technique currently available for use by patients involves using a spring loaded lancet to stab 16 17 the finger to obtain a blood sample which is transferred to a glucose test strip. The concentration 18 19 is derived either by reading the test strip with a 20 reflectance meter or by visual comparison of colour 21 change against a colour scale. Many diabetics find the 22 testing onerous as the technique is painful, 23 inconvenient, messy, potentially embarrassing and 24 offers a site for the transmittance and acceptance of infection. 25

Techniques have also been developed for non invasive 1 measurement using transmittance or reflectance 2 spectroscopy. However the required instruments are 3 expensive and it is difficult to obtain accurate and repeatable measurements. 6 There are also known various types of in vivo chemical 7 These rely on implanting minimally invasive 8 sensors under the skin surface, but such sensors have 9 poor long term reproducibility and bio-compatibility 10 problems. 11 12 There is therefore a need for improved means for 13 routine monitoring of blood glucose in a manner which 14 is simple and straightforward to use. 15 16 The present invention makes use of photoacoustic 17 The fundamentals of photoacoustic 18 techniques. techniques are well known per se. A pulse of light, 19 typically laser light, is applied to a substance 20 containing an analyte of interest in solution or 21 dispersion, the wavelength of the applied light being 22 chosen to interact with the analyte. Absorption of the 23 light energy by the analyte gives rise to microscopic 24 localised heating which generates an acoustic wave 25 which can be detected by an acoustic sensor. 26 techniques have been used to measure physiological 27 parameters in vitro. 28 29 US Patents 5348002 and 5348003 (Caro) propose the use 30 of photoacoustics in combination with photoabsorption 31 for the measurement of blood components in vivo. 32 However, the arrangement proposed by Caro has not been 33 demonstrated as a workable system and may suffer from 34 interference to a degree which would preclude useful 35 acoustic signals, and since they would also suffer from 36

interference and resonance effects from hard structures 1 2 such as bone. 3 4 It has also been proposed by Poulet and Chambron in Medical and Biological Engineering and Computing, 5 November 1985, Page 585 to use a photoacoustic spectrometer in a cell arrangement to measure 7 characteristics of cutaneous tissue, but the apparatus 8 9 described would not be suitable for measuring blood 10 analytes. 11 12 Published European Patent Application 0282234A1 13 (Dowling) proposes the use of photoacoustic spectroscopy for the measurement of blood analytes such 14 as blood glucose. This disclosure however does not 15 show or suggest any means which would permit the 16 required degree of coupling to body tissues for use in 17 18 vivo. 19 Accordingly, the present invention provides a sensor 20 head for use in photoacoustic in vivo measurement, 21 22 comprising a housing shaped to engage a selected body part, light transmission means terminating in said 23 24 housing so as to transmit light energy from a light 25 source to enter the body part along a beam axis, and acoustic transducer means mounted in the housing to 26 27 receive acoustic waves generated by photoacoustic 28 interaction within the body part, the acoustic transducer means being disposed in the housing to 29 receive said acoustic wave in a direction of high 30 31 acoustic energy. 32 The expression "direction of high acoustic energy" is 33 used herein to denote a direction other than the 34 35 forward direction of the light beam. Preferably, the

transducer means is disposed so as to intercept

acoustic energy propagating at right angles to the 1 optical beam axis, or at an angle to the optical beam 2 axis which may be down to about 20°, typically about 45°. 5 An exact measure of the angle of high acoustic energy 6 can be worked out but is dependent upon the specific 7 geometry of the light source, the properties of the 8 tissue and the absorption coefficient of the tissue. 9 One model for understanding the propagation of the 10 acoustic energy in any homogenous media was developed 11 by Huyghens and is called the principle of 12 In this model each volume element that 13 superposition. is illuminated by the light generates an acoustic 14 pressure wave that radiates outward in a spherical 15 16 The magnitude of the pressure wave at each volume element depends on the intensity of the optical 17 beam at that location, the absorption coefficient of 18 the material at that location, the wavelength of light 19 20 and on several other physical properties of the material such as the speed of sound and the specific 21 22 The signal measured at the detector is just the 23 superposition of all pressure waves from all points that are illuminated by the source light. 24 analytical solution for the pressure wave has been 25 26 worked out for a few cases in aqueous material. analytical case that best matches the in-vivo 27 28 measurements is that of a cylindrical optical beam 29 propagating in a weekly absorbing material. In this 30 case the direction of highest acoustic energy is The base detector 31 perpendicular to the optical axis. location is with the plane of the detector 32 perpendicular to the acoustic energy, or parallel to 33 34 the optical axis. This is because the acoustic

detector has the highest sensitivity when the acoustic

energy strikes the detector perpendicular to the plane

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1 of the detector. This analytical model is not 2 completely accurate for the in-vivo measurement case because of scattering of the tissue and because the 3 tissue absorbs more than the model predicts. differences indicate that a different position for the 5 detector will be optimal. A detailed numeric model is required to determine the best detector location and is 7 8 dependent upon the beam properties (focused to a point, colligated, etc.), body site (finger, earlobe, arm 9 10 etc.) and wavelength. One skilled in the art can readily develop an appropriate mode. However, suitable 11 locations for a detector will generally be at an angle 12 13 to the optical axis. Angles between 40 and 90 degrees should be suitable. 14 15 16 In one preferred arrangement, the acoustic transducer means is arranged parallel to the optical beam axis. 17 This arrangement is particularly suitable for use where 18 19 the selected body part is the distal portion of a 20 finger, in which case the housing may include a 21 generally half-cylindrical depression in which the 22 finger may be placed with the light transmission means 23 aimed at the end of the finger. 24 25 Preferably, the acoustic transducer means comprises a 26 piezoelectric transducer which most preferably is of a 27 semi-cylindrical shape. This transducer may be provided with a backing of lead or other dense 28 29 material, and the backing may have a rear surface 30 shaped to minimise internal acoustic reflection. 31 32 Alternative transducer means include a capacitor-type 33 detector, which is preferably small and disk-shaped; an 34 integrated semiconductor pressure sensor; and an 35 optical pressure sensor, for example based on an

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optical fibre.

In an alternative arrangement, the plane of the 1 transducer may be arranged to be perpendicular to the 2 optical axis to detect the acoustic wave which is 3 propagating in a direction opposite to the direction of the light beam. For example, the acoustic transducer means may be part-spherical with an aperture to allow access for the light beam. This may be particularly 7 suitable for engagement with a body part other than the 8 finger, for example the back of the arm. 9 10 The generation of a surface acoustic wave is an 11 inherent aspect of the in vivo pulsed photoacoustic 12 generation in tissue and may be used to characterize 1.3 A surface wave tissue properties such as density. 14 detector may be provided in the sensing head assembly. 15 16 Preferably means are provided for ensuring a consistent 17 contact pressure between the selected body part and the 18 In the case where the acoustic transducer means. 19 selected part is the distal portion of the finger, said 20 means may be provided by mounting the portion of the 21 housing engaged by the finger in a resiliently biased 22 fashion against the remainder of the housing, and 23 providing means to ensure that measurement is effected 24 when the predetermined force or pressure is applied by 25 the subject against the resilient bias. In the case 26 where the selected part is the earlobe, said means may 27 be provided by placing the ear between two plates and 28 applying pressure to the ear with springs or weights or 29 The two plates holding the ear may 30 other force method. The two plates may be flat contain a removable insert. 31 or may be of another shape to optimally position the 32 detector with respect to the beam axis. 33

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In addition, the present invention provides a sensor 35 head for use in photoacoustic in-vivo measurements, 36

comprising a housing shaped to receive a removable 1 insert, a removable insert that engages a selected body 2 part, the insert being fitted to an individual, 3 allowing for a range of sizes of body parts to be used, 4 and further comprising light transmission means 5 terminating in or near said removable insert so as to 6 transmit light energy from a light source or sources to 7 enter the body part along a beam axis, and an acoustic 8 transducer means mounted in the housing or in the 9 removable insert to receive acoustic waves generated by 10 photoacoustic interaction within the body part to 11 receive said acoustic waves in a direction of high 12 acoustic energy. 13 14 From another aspect the present invention provides an 15 in vivo measuring system comprising a sensor head as 16 hereinbefore defined in combination with a light source 17 coupled with the light transmission means, and signal 18 processing means connected to receive the output of the 19 acoustic transducer means and to derive therefrom a 20 measurement of a selected physiological parameter. 21 22 Preferably, the light transmission means is a fiber 23 distribution system where each light source is 24 connected to an individual fiber and when multiple 25 light sources are used the multiple fibres are joined 26 by some standard fiber combining method, such as a 27 wavelength division multiplexer or a fiber coupler. 28 The fiber that comes from the light source, or contains 29 the combined light for a multiple source system, is 30 then terminated in proximity to the body part being 31 The fiber could be in contact with the body measured. 32 part or alternatively standard optics, such as lenses, 33 beamsplitters and such, could be employed to convey the 34 light from the end of the fiber to the body part.

reference detector or several reference detectors and

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beamsplitters can be added to the optical distribution system to determine the energy of the light entering the body part.

Alternatively, the optical distribution system may contain mechanical holders, lenses and such to convey the light from the source, or sources, to a location in proximity to the body part being measured. A reference detector or several reference detectors and beamsplitters can be added to the optical distribution system to determine the energy of the light entering the body part.

The acoustic signal from the detector contains information in both time and frequency, and there may be information from several sources. The processing means is preferably a multi-dimensional processing method, such as Classical Least Squares (CLS) or Partial Least Squares (PLS). Alternatively the processing method may be more flexible, such as a In addition to these methods the Neural Network. signals may be analysed for their frequency content using such techniques as Fourier Analysis or Frequency In addition techniques may be employed that use time information such as the time delay from source Techniques that combine both frequency and time information may be employed, such as Wavelet analysis.

The light source is preferably a laser light source and is most suitably a pulsed diode laser, but may utilise a set of such lasers or utilise a tunable laser source. In a particularly preferred form, suitable for use in measuring blood glucose concentration, a laser diode is used with a wave length in the range of approximately 600 nm to 10,000 nm and a pulse duration of the order

of 5 to 500 ns. 1

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The delivery to the measurement site may be either 3 directly or by optical fibre with a suitable optical 4 element to focus the beam into the tissue. 5

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Preferably means are provided for time multiplexing multiple sources when multiple sources are used. Each source is switched on, and it generates an optical pulse, or a set of optical pulses. This pulse, or set of pulses, generates an acoustic signal that is Each source is pulsed in detected by the detector. sequence until all sources have been used to generate their own signal.

14 15 16

17

18

The measuring system may conveniently be in the form of a self contained system including a power supply and a readout, which may be carried on the person and used at any convenient time.

19 20 21

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It is also possible for such a self contained system to incorporate, or to be provided with facilities for connection to, a cellular telephone, two-way pager or other communication device for routine transmission of measurements taken to a central data collection point.

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In addition the measuring system may have provision for manipulating the body part under measurement and for performing additional measurement of the tissue to get other information about the state of the physiology of the issue. It is well-known in the art that squeezing a section of tissue to increase the pressure and then releasing the pressure will cause changes in the total blood volume in the measurement site. The present invention may allow for this type of manipulation

35 including the squeezing of a body part, such as an 36

earlobe, and making photo acoustic measurements at 1 The present invention may several different pressures. 2 also allow for the measurement of the temperature of 3 the body site and to apply a correction to the measurements based upon the temperature of the body site. 7 Another type of physiological manipulation is body 8 It is known in the art that several temperature. 9 parameters involved in the detection of the photo 10 acoustic signal, such as the speed of sound, are 11 dependent upon the temperature of the medium the signal 12 is propagating through (the tissue). Also the 13 profusion of the blood in the small capillaries is 14 dependent upon the temperature of the tissue. 15 Additional information about the tissue can be obtained 16 if the photo acoustic measurement is made at several 17 temperatures, both higher and lower than ambient 18 This additional information is used to temperature. 19 better eliminate interferences to the determination of 20 These are only two the analyte under investigation. 21 examples of manipulating the body site and are not 22 intended to be an exhaustive list, and they can be used 23 in combination with other manipulation techniques. 24 25 The in-vivo measuring system may comprise a means for 26 storing calibration coefficients or operation 27 parameters or both calibration coefficients and 28 operational parameters, in order to calibrate the 29 instrument and to set critical operational parameters. 30 31 Another aspect of the present invention provides a 32 means for adjusting the calibration coefficients and 33 operational parameters to be specific to a particular 34 person and may be used to adjust for such things as 35 body part size, skin color, skin condition, amount of 36

body fat, efficiency of the detector and efficiency of 1 2 the source(s). In addition the present invention may provide for having the specific calibration coefficients and 5 operational parameters be contained in a storage site 6 This allows for the located in the removable insert. 7 system to be both mechanically and operationally 8 configured to a particular individual. Additionally 9 the invention may allow for the calibration 10 coefficients and operational parameters to be stored in 11 two locations, one in the non-removable housing and one 12 in the removable insert with some of the coefficients 13 and parameters stored in each location. This allows 14 for reader system coefficients to be stored in the 15 reader and coefficients specific to an individual to be 16 stored in the removable insert for that person, 17 enabling many people to use the same reader. 18 19 Another aspect of the present invention provides means 20 for connecting the non-invasive measuring system to an 21 invasive measuring system for the purpose of 22 calibrating or adjusting the operational parameters of 23 Such connection may the non-invasive measuring system. 24 be accomplished, but is not limited to, communication 25 by a wire, IR link or radio waves. 26 27 Another aspect of the present invention provides a 28 29 method for removing instrument drift from the

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 Placing a standard in the reader in place of the body part.

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Measuring the signal from the standard for each
 wavelength and storing the values in the

measurement comprising the steps of:

1		calibration storage location.
2	_	- a hadronart
3	3.	Before making a measurement of a body part,
4		placing the calibration standard in the reader.
5		and the second second for each
6	4.	Measuring the signal from the standard for each
7		source.
8		
9	5.	Comparing the just measured standard values to the
10		stored calibration values.
11		
12	6.	Calculating correction factors for each source
13		wavelength.
14		
15	7.	Removing the standard and placing the body part in
16		the reader.
17		
18	8.	Measuring the signal from the body part for each
19		source.
20		
21	9.	Adjusting the measured values using the calculated
22		correction factors.
23		
24	In a	ddition to the signal correction factors a
25	corr	ection factor can be calculated for the instrument
26	temp	erature. This can be applied to each signal with a
27	diff	erent correction coefficient.
28		
29	The	invention further provides a method of measuring a
30	biol	ogical parameter in a subject, the method
31	comp	rising the steps of:
32		
33		directing one or more pulses of optical energy
34		from the exterior into the tissue of a subject
35		along a beam axis, the optical energy having a
36		wavelength selected to be absorbed by tissue

1	components of interest, thereby to produce a
2	photoacoustic interaction;
3	
4	detecting acoustic energy resulting from said
5	photoacoustic reaction by means of a transducer
6	positioned to intercept acoustic energy
7	propagating in a direction other than the forward
8	direction of said beam axis; and
9	
10	deriving from said detected acoustic energy a
11	measure of the parameter of interest; and a
12	corresponding apparatus.
13	
14	
15	Embodiments of the invention will now be described, by
16	way of example only, with reference to the accompanying
17	drawings in which:-
18	
19	Figs. 1A,1B and 1C are side views illustrating the
20	principle of operation of one embodiment of the
21	present invention;
22	
23	Fig. 2 is a schematic perspective view showing a
24	sensor head for use in carrying out the
25	measurement illustrated in Fig. 1;
26	
27	Fig 3. is a cross section view of the sensor head
28	of Fig. 2;
29	
30	Fig. 4 is a side view of the sensor head of Fig.
31	2;
32	
33	Fig. 5 is a schematic perspective view of an
34	apparatus incorporating the sensor head of Figs. 2
35	to 4;
36	

1	Fig. 6 is a perspective view illustrating an
2	alternative form of sensor head;
3	
4	Fig. 7 is a schematic end view showing another
5	form of sensor head;
6	
7	Figs. 8a and 8b are a cross-sectional side view
8	and a plan view, respectively, of a further sensor
9	head;
10	
11	Fig. 9 is a cross-sectional side view of one more
12	embodiment of sensor head;
13	
14	Fig. 10 is a perspective view of one type of ear
15	interface apparatus;
16	
17	Fig. 11 is a schematic of a multiple laser optical
18	distribution system using lenses, mechanical
19	mounts and a reference detector;
20	
21	Fig. 12 is a schematic of a multiple laser optical
22	distribution system using fiber optic cables and a
23	fiber Wavelength Division Multiplexer (WDM), a
24	beam splitter and a reference detector;
25	
26	Fig. 13 is a perspective view of a finger
27	interface apparatus with removable inserts that
28	are moulded to fit one individual;
29	
30	Fig. 13A shows part of the apparatus of Fig. 13 in
31	greater detail;
32	
33	Fig. 14 is a schematic of a semi-spherical
34	detector that contains a hole for the light beam,
35	with a vacuum system and a fiber distribution
36	system;

1	
2	Fig. 15 is a perspective view showing one form of
3	the instrument utilizing the vacuum body
4	interface, a semi-spherical detector and the
5	multiple laser source with lenses and mechanical
6	housing;
7	
8	Fig. 16 is a perspective view showing one form of
9	the instrument using an ear lobe body interface,
10	with the added feature of being able to manipulate
11	the pressure on the ear lobe; and
12	
13	Figs. 17, 18 and 19 are graphs illustrating an
14	example.
15	
16	Referring to Fig 1, an important feature of the present
17	invention lies in introducing light energy along an
18	axis into an area of soft tissue and detecting the
19	resulting acoustic response transverse to that axis.
20	Accordingly, in the arrangement of Fig 1A light energy
21	from a diode laser (not shown) is transmitted via a
22	fibre-optic guide 10 to the tip of a finger 12. The
23	photoacoustic interaction occurs in an approximately
24	cylindrical region indicated at 14 from which acoustic
25	energy is radiated in a generally cylindrical manner
26	and is detected by a transversely arranged acoustic
27	transducer 16.
28	
29	In Figs 1B and 1C, the principle is similar. The
30	finger 12 is pressed against a support with force F.
31	In Fig 1B, the incident light beam indicated at L is
32	directed as in Fig 1A, and the transducer 16 is at an
33	angle of 45 degrees thereto. In Fig 1B, the angle is
34	90 degrees as in Fig 1A, but the incident beam is
35	directed differently into the fingertip.

In the present embodiment, the laser wavelength is chosen to achieve high degree of absorption by glucose present in the blood. A suitable wavelength is in the range approximately 1000 to 3000 nm. The laser pulse duration is chosen to be short, typically of the order of 5 to 500 ns, in order to minimise thermal diffusion and thus to optimise the acoustic waveform. same reasons, it is desirable to use a spot size which is sufficiently small to minimise thermal diffusion, typically a spot size of the order of 0.05 mm to 0.50 mm. 

The efficiency of the photoacoustic detection is also influenced by the positioning and dimensions of the acoustic transducer in relation to the characteristic extinction length of the tissue at the principal wavelengths chosen for measurement. In the fingertip arrangement of Fig. 1, the system efficiency will be improved by optimising the length of the transducer crystal parallel to the axis of the finger, but the length should not be so great as to give rise to undesired signals which would occur at the point of entry of the optical energy into the finger and by reason of interaction of the acoustic energy with bone or other hard tissue.

A second limit on the size of the acoustic detector derives from the wavelength of the acoustic wave in the tissue. Again making use of Huyghens principal of superposition we view each point of tissue, that is illuminated by the incoming light, as a point source that generates a spherical pressure wave. The signal measured at the detector is just the superposition of all pressure waves from all points that are illuminated by the source light. Normally if the size of the detector is increased then the signal should also

increase because more energy is received by the 1 detector. However if the acoustic detector is too 2 large then a pressure wave generated from a tissue 3 4 element will create a pressure wave that will strike the both ends of the detector. If the paths length 5 6 from the tissue element to the first end of the detector is different than the path length to the 7 8 second end of the detector and if this difference in 9 path length is about one half of the acoustic signal wavelength then the signal will destructively interfere 10 with itself and will reduce the magnitude of the 11 measured signal. 12 14 Referring to Fig 2, one manner of carrying out the 15 arrangement shown in Fig 1 makes use of a sensor head

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having a finger rest 18 which is slidably moveable 16 within housing 20 closed by a front plate 22. 17 inserts his finger in a semi-cylindrical depression 24 18 in the finger rest 18 with the finger tip engaged 19 against an end surface 28 which includes an exit face 20 21 26 of the optical fibre 10. The finger is then pressed 22 downwardly against a resilient bias to enable a 23 standardised contact to be obtained between the skin and the acoustic transducer. The finger tip may first 24 be dipped in water or coated with an aqueous gel to 25 26 improve the acoustic coupling.

27

28 Referring to Figs 3 and 4, in this preferred 29 arrangement the acoustic transducer comprises a semi-30 cylindrical piezoelectric transducer 30. 31 transducer 30 is provided with a backing member 32 of 32 lead or another dense substance, the rear face 34 of The use of the 33 which is shaped in irregular curves. 34 semi-cylindrical transducer 30 maximises the area for 35 reception of acoustic energy from the finger, while the 36 use of a dense backing material minimises ringing

effects within the transducer. Additionally, the rear face 34 is shaped as shown to reduce reflection of acoustic energy back towards the piezo crystal.

Fig 3 also shows the finger rest biased upwardly by the use of constant tension springs 38.

Fig 5 illustrates schematically the apparatus of Figs. 2 and 3 embodied in a self-contained, portable blood monitoring apparatus including a user readout 40. An apparatus of this nature allows a diabetic to monitor blood glucose concentration in a convenient manner, as frequently as may be desired, and in a painless and discreet manner.

Other forms of photoacoustic sensor head are possible within the scope of the present invention. For example, Fig. 6 shows an arrangement in which a light guide 50 and an acoustic transducer 52 are applied to a finger 54 by means of a hinged clamp member 56. Fig. 7 shows a finger 60 engaged by a light guide 62 and an acoustic transducer 64 which are carried on a moveable assembly 66 with the finger 60 being trapped between the moveable assembly 66 and a fixed anvil 68.

 It is also possible to arrange the sensor head to cooperate with a soft tissue surface of the body, for
example a soft part of the abdomen. Figs. 8a and 8b
show an arrangement in which a cup shaped member 70,
suitably of rubber, causes a light guide 72 and an
acoustic transducer 74 to be contacted with a bulge of
soft tissue 76 which may for example be drawn into
contact by means of a partial vacuum within the member
70 caused by suction through a conduit 78, or by other
mechanical or adhesive means.

A somewhat similar arrangement is shown in Fig. 9 in which a planar mount 80 carrying a light guide 82 and acoustic transducer 84 is secured to a soft area of body by means of surgical adhesive 86.

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Referring to Fig. 10, one method of performing measurement on an ear lobe involves placing the ear lobe between a fixed plate 87 and a movable plate 88. The acoustic detector 89 is mounted partially perpendicular that is at an acute angle, to the beam axis defined as line going from the center of a lens 90 It has been found that to the center of a window 91. the system works satisfactorily with the detector 89 at an angle or 45° to the beam axis. The window 91 and the detector 89 are placed in direct contact with the ear and the opposite plate 88 places pressure on the ear using a suitable mechanism (not shown). particular embodiment of the ear interface apparatus incorporates an alignment ring 92 which is temporarily attached to the ear and fits over the window housing 91 to aid in aligning ear into the same location every time.

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31 32 Referring to Fig. 11, one method of combining light sources into the instrument is to use a mechanical housing 93 with several holes used to align lenses 95 and laser diodes 94. The housing shown uses a hexagonal array of seven holes. The sources and lenses are arranged in such a way that they all focus to the same location 96 which could be on the surface of the body part. This design does not show the inclusion of beamsplitters and reference detectors but they can be added in an alternative arrangement.

33 34

An alternative method of combining several sources into one beam is shown in Fig. 12. Several laser diodes 97

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are shown coupled to individual fiber optic cables 131.
1
 2
      These cables 132 are combined using a fiber Wavelength
      Division Multiplexer (WDM) 98. Alternative combination
 3
      methods exist including couplers and multi-fiber
                The combined light exits the WDM 98 in a
      single fiber 104 and terminates at the focal point of a
 6
                 This end of the fiber is imaged to the end
      lens 131.
      of the finger 103 to a spot 102 using another lens 130.
8
      Some of the light is split off the main beam using a
9
      beam splitter 100 and focused onto a reference detector
10
      101 using another lens 99. Additional reference
11
      detectors and/or beamsplitters can be added to the
12
      distribution system without changing its function.
1.3
      Alternatively a reference detector could look directly
14
      at the body part to measure the light reflecting off
15
      the surface, as a measure of the overall light energy
16
17
      entering the body part.
18
      Referring to Fig. 13, another method of using a finger
19
      as the body part and including removable inserts is
20
      shown. A finger 105 is inserted into an insert 106
21
      that is used to customize the finger holder to a
22
                          The moulded insert 106 is placed
23
      particular finger.
                           The finger 105 is placed against a
24
      into a housing 107.
      semi-cylindrical acoustic detector in a module 108 which
25
      is also attached to the housing 107. A cover 109 for
26
      the housing 107 contains a mechanism 111 to apply
27
      constant force to the finger 105. The light beam 110
28
      is introduced into the finger 105 using a suitable
29
      optical distribution system (not shown). Fig. 13A shows
30
      the module 108 in greater detail. A base 200 carries a
31
      part-cylindrical piezo transducer 202 on a support 204.
32
      206 indicates a coaxial connector to communicate the
33
34
      transducer signal.
```

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Fig. 14 shows a schematic of an alternative to the

vacuum arrangement shown in Figs. 8 and 9. In this 1 2 system a photoacoustic reader 121 is placed against the skin 113 with a semi-spherical detector 112 in contact 3 with the skin 113. A vacuum pump 115 and vacuum seal 4 5 116 create a negative pressure and pull the skin 113 against the detector 112. Processing electronics 119 6 7 energizes light sources 118 and an optical distribution system 117 routes the light to the body part through a 8 hole in the top of the semi-spherical detector 112. 9 10 The optical distribution system 117 directs a small portion of the light to a reference detector 114. 11 processing electronics 119 measures the signal from the 12 acoustic detector 112 and the reference detector 114 13 for each optical source 119 and calculates the glucose 14 The value is displayed on a display 120. 15 value. 17 Fig. 15 shows a similar system 125, only using another 18

16

type of optical distribution system 127. vacuum pump 123 creates a negative pressure which draws 19 20 the skin up to an acoustic detector 122. Processing electronics 124 signals light sources in optical 21 distribution system 127 to illuminate and a signal is 22 23 generated at acoustic detector 122. The processing 24 electronics 124 calculates the proper value and displays it on a display 126. 25

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Fig. 16 shows an alternative arrangement of a photoacoustic reader. In this system 128, the vacuum system is replaced with an ear squeeze mechanism 129 which applies pressure to the ear. An acoustic detector 130 detects the signals from the ear lobe.

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In the most straightforward forms of the invention, a single analyte such as glucose in blood can be measured by using light of selected wavelengths and by measuring the area or the amplitude of the received acoustic

pulse. It is preferable to make each measurement by 1 using a train of pulses, for example about 100 pulses, 2 and averaging the results in order to minimise the effects of noise and pulse effects in the blood flow. 4 5 The accuracy of the detection system is governed, in 6 part, by the Signal to Noise Ratio (SNR) of the system. 7 Variations in the intensity and duration of the light 8 source can cause the acoustic signal to contain 9 variations. A normalization technique, such as taking 10 the ratio of the acoustic signal to the optical signal, 11 can significantly reduce the effect of the source 12 variations, thereby improving the signal to noise ratio 13 The optical signal can be measured with 14 of the system. a reference detector, or several reference detectors, 15 one for each source or one for a wavelength range. 16 equation describing this type of normalization follows: 17 18 19 Acoustic Signal 20 Normalized Signal Optical Signal 21 22 23 In some cases the relationship between the optical 24 signal land the acoustic signal changes with wavelength 25 and light intensity. When this is the case the 26 accuracy of the measurement can be further enhanced by 27 determining the energy dependence of the photoacoustic 28 This may be determined by establishing the 29 specific relationship between the photoacoustic signal 30 land the incident energy from a set of measurements and 31 using this relationship to compensate for the non 32 linear response. An equation describing this type of 33 normalization is as follows: 34 35 Acoustic Signal Normalized Signal = 36

1 Scaling Factor \*Optical Signal + Offset. 2 3 4 Other normalization methods can also apply. 5 interval between the optical pulse and the detection of the acoustic signal may be used to characterise 6 7 physical properties such as the velocity of sound in 8 the tissue. In addition, in another embodiment of the device the damping of the acoustic oscillations may be 9 10 used to monitor the elastic properties of the tissue 11 and, in particular, the compressibility. Both of these 12 aspects may be used in the person to person calibration 13 of the photoacoustic response. 14 15 More complex analysis of the received acoustic energy is possible. For example, a time-gating technique may 16 17 be used to derive measurement at varying depths within 18 the tissue being examined. Alternatively, an array of 19 detectors can be employed to determine the profile of 20 the absorption of the acoustic signal at different 21 depths and locations. This depth profile will change 22 with the absorption coefficient and could be used as 23 additional information to determine the analyte 24 concentration. It is also possible to derive 25 information relating to a number of analytes of 26 interest by more sophisticated analysis of the received 27 acoustic energy wave forms, for example by analysis of 28 the frequency spectrum by Fourier transform or wavelet 29 analysis techniques. 30 31 Alternatively, or in combination with the frequency 32 techniques and multiple detectors, multiple light 33 sources can aid in the determination of the 34 concentration of a number of analytes. 35 36 There are a number of tissue features which may vary

from person to person or with in the same person over time which impact the photoacoustic signal observed. To obtain an accurate measurement of a given analyte, such as glucose, it may be helpful to also determine the concentration of other analytes such as haemoglobin which may act as interferants. One approach is to generate several distinct photoacoustic signals using excitation light of several different wavelengths. example, excitation light of a wavelength of which haemoglobin absorbs strongly but glucose has little if any absorption could be sued to obtain a measure of the haemoglobin concentration with which to normalize the effect of haemoglobin on measurements made on different persons or on the same person at different times. These measurements which are to be normalized might be based on the photoacoustic signal generated by light of a wavelength at which glucose absorbs.

It is also possible to measure the concentration of such interferants by other means, such as infrared light absorption, and thus normalize or correct the photoacoustic signal representative of the desired analyte for variations in these interferants. Thus, for example, the photoacoustic signal representative of glucose could be corrected for variations in haemoglobin concentration determined by optical absorption techniques such as those taught in US Patent No 5,702,284.

For the reliable and reproducible determination of glucose a signal to noise ratio of at least 10,000 is recommended. In this regard water is typically present in human tissue of a concentration of about 50 molar while glucose is present at a concentration of about 5 millimolar in a normal individual.

Apparatus and method embodying the present invention

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2 have been found to yield accurate and repeatable 3 results. In the case of blood glucose measurement, the clinical range of glucose concentration is approximately 5-10 m mol/l in healthy subjects, and up to 40 m mol/l in diabetics. An analysis based on 6 simple absorption models suggests that the change in photoacoustic signal over this range might be as little 8 as 0.2%. The present invention has been found to 9 provide a change in photoacoustic signal of up to 140% 10 for a change in glucose concentration of 15m mol/1. 11 12 The precise mechanisms involved are not at present 13 14 fully understood. It is believed, however, that 15 absorption occurs primarily in body plasma and is modified by the presence of glucose, and that this 16 17 affects beam geometry. 18 19 Example 20 21 The blood glucose levels of three individuals, one normal individual, one type 1 diabetic and one type 2 22 23 diabetic, were followed over a two hour period 24 following each individual taking about 75 grams of 25 glucose orally in an aqueous solution by both 26 photoacoustics and direct blood measurement. 27 results are reported in Figures 17, 18 and 19. 28 Photoacoustic measurements were made every five minutes 29 and blood measurements were made very ten minutes. 30 blood samples were venous blood samples analysed by the 31 standard glucose oxidase method using a Yellow Springs 32 instrument. The error bands for the blood measurements 33 were derived from the literature accompanying the 34 testing instrument while those for the photoacoustic

results were based on the averages taken over 1000

The results were obtained from a configuration

similar to that illustrated in Figure 1 in which 10 was an end of a 1 km multimode fibre optic cable which was placed against the finger 12. The other end received 600 nanosecond pulses of 1040 nanometer light from a Q switched Nd:YAG laser delivering 2,7 micro joules per pulse for each measurement. Raman interactions in the fibre caused the production of light an additional wavelengths as set forth in the following table:

Wavelength in nm	Average pulse energy in microJoules	Pulse width in ns	Approximate bandwidth in nm
1064	2.7	600	4
1120	2.25	500	6
1176	2.0	450	8
1240	1.5	425	12
1308	0.85	400	15
1390	0.3	350	20
1450	0.1	350	20
1500	0.2	350	20
1550	0.18	360	20

The resulting photoacoustic signal was detected by a 5mm disc transducer with a lead backing and fed to an amplifier and an oscilloscope. The transducer was generally placed as 16 in Figure 1 but was not

precisely parallel to the beam axis; its detection 1 plane was at an angle of about 20 degrees to the beam 2 The photoacoustic signal was evaluated in terms 3 of the difference in voltage signal from the positive peak of the compression to the negative peak of the relaxation of the acoustic pulse. The change in photoacoustic response correlated well Я with the change in blood glucose concentration over the 9 two hour measurement period. A correlation of 0.89 was 10 achieved on samples ranging from 4 to 35 m mol/1. 11 12 Other modifications and improvements may be made to the 13 foregoing embodiments within the scope of the present 14 invention as defined in the claims. 15

## CLAIMS

1 2

A sensor head for use in photoacoustic in vivo 1. 3 measurement, comprising a housing shaped to engage 4 a selected body part, light transmission means 5 terminating in said housing so as to transmit 6 light energy from a light source to enter the body 7 part along a beam axis, and acoustic transducer 8 means mounted in the housing to receive acoustic 9 waves generated by photoacoustic interaction 10 within the body part, the acoustic transducer 11 means being disposed in the housing to receive 12 said acoustic wave in a direction of high acoustic 13 14 energy.

15

A sensor head according to claim 1, in which the
 acoustic transducer means is arranged at least
 partially perpendicular to the optical beam axis.

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21 3. A sensor head according to claim 2, for use where 22 the selected body part is the distal portion of a 23 finger, in which the housing includes a generally 24 half-cylindrical depression in which the finger 25 may be placed with the light transmission means 26 aimed at the end of the finger.

27

4. A sensor head according to any preceding claim, in which the acoustic transducer means comprises a piezoelectric transducer which is of a semicylindrical shape.

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33 5. A sensor head according to any preceding claim, in 34 which the acoustic transducer means comprises a 35 piezoelectric transducer which is provided with a 36 backing of lead or other dense material. 1 6. A sensor head according to claim 5, in which said 2 backing has a rear surface shaped to minimise 3 internal acoustic reflection.

4

7. A sensor head according to any of claims 1 to 4, in which the transducer means comprises a capacitor-type detector.

8

9 8. A sensor head according to any of claims 1 to 4,
10 in which the transducer means comprises a
11 piezoelectric transducer arranged generally
12 perpendicular to the optical axis to detect the
13 acoustic wave which is propagating in a direction
14 opposite to the direction of propagation of the
15 light beam.

16

9. A sensor head according to claim 8, in which the transducer is part-spherical with an aperture to allow access for the light beam.

20

10. A sensor head according to any preceding claim,
 including a surface wave detector for
 characterizing tissue properties.

24

25 11. A sensor head according to any preceding claim,
26 including means for ensuring a consistent contact
27 pressure between a selected body part and the
28 acoustic transducer means.

29

12. A sensor head according to claim 11, for use where
the selected part is the distal portion of a
finger, said means being provided by mounting a
portion of the housing engaged by the finger in a
resiliently biased fashion against the remainder
of the housing, and providing means to ensure that
measurement is effected when a predetermined force

or pressure is applied by the subject against the resilient bias.

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13. A sensor head according to claim 11, for use where the selected part is the earlobe, said means being provided by two plates, between which the earlobe may be placed, and means for pressing the plates together to apply pressure to the ear.

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A sensor head for use in photoacoustic in-vivo 10 14. measurements, comprising a housing shaped to 11 receive a removable insert; a removable insert 12 that engages a selected body part, the insert 13 being fitted to an individual, allowing for a 14 range of sizes of body parts to be used; light 15 transmission means terminating in or near said 16 removable insert so as to transmit light energy 17 from a light source to enter the body part along a 18 beam axis; and an acoustic transducer means 19 mounted in the housing or in the removable insert 20 to receive acoustic waves generated by 21 photoacoustic interaction within the body part, 22 the acoustic transducer means being disposed in 23 the housing or insert to receive said acoustic 24 waves in a direction of high acoustic energy. 25

26

An in vivo measuring system comprising in 27 15. combination: a sensor head as claimed in any 28 preceding claim; a light source coupled with the 29 light transmission means; and signal processing 30 means connected to receive the output of the 31 acoustic transducer means and to derive therefrom 32 a measurement of a selected physiological 33 34 parameter.

35 36

16. The system of claim 15, in which the light

transmission means is a fiber optic distribution 1 2 system. The system of claim 16, in which there is a 4 17. plurality of light sources each connected to an 5 individual fiber and the respective fibers are 6 joined by a wavelength division multiplexer or a 7 fiber coupler. 8 9 The system of claim 16 or claim 17, in which the 10 18. fiber optic distribution system terminates in 11 contact with the body part. 12 13 The system of claim 16 or claim 17, in which the 14 19. fiber optic distribution system communicates with 15 the body part via optical elements such as lenses 16 and beamsplitters. 17 18 20. The system of claim 15, in which the light 19 transmission means comprises optical elements 20 mounted in mechanical holders and arranged to 21 convey the light from the light source to a 22 location in proximity to the body part. 23 24 The system of claim 19 or claim 20, in which the 25 21. light transmission means includes at least one 26 beamsplitter arranged in the light path to direct 27 a portion of the light to a respective reference 28 detector to measure the energy of the light 29 entering the body part. 30 31 The system of any of claims 15 to 21, in which the 22. 32 signal processing means is adapted to perform a 33

36 23. The system of claim 22, in which the signal

34 35 multi-dimensional processing method.

7		processing means is adapted to perform one of
2		Classical Least Squares or Partial Least Squares.
3		
4		
5	24.	The system of any of claims 15 to 21, in which the
6		signal processing means comprises a Neural
7		Network.
8		
9		$\cdot$
10	25.	The system of any of claims 15 to 24, in which the
11		signal processing means is operable to analyse the
12		signals for their frequency content using one of
13		Fourier Analysis and Frequency Filtering.
14		
15	26.	The system of any of claims 15 to 25, in which the
16		signal processing means additionally applies
17		techniques that use time information.
18		
19	27.	The system of claim 26, in which the time
20		information processed is the time delay from
21		source trigger.
22		
23	28.	The system of any of claims 15 to 25, in which the
24		signal processing means additionally applies
25		techniques that combine both frequency and time
26		information.
27		
28	29	The system of claim 28, in which the signal
29		processing means performs wavelet analysis.
30		
31	30.	The system of any of claims 15 to 29, in which the
32		light source is a laser light source.
33		
34	31.	The system of claim 30, in which said laser light
35		source is selected from a pulsed diode laser, a
36		set of pulsed diode lasers, and a tunable laser

1 source.

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32. The system of claim 31, for use in measuring blood glucose concentration, in which the light source is a laser diode with a wavelength in the range of approximately 600 nm to 10,000 nm and a pulse duration of the order of 5 to 500 ns.

8

9 33 The system of any of claims 30 to 32, in which the 10 light transmission means is arranged to produce a 11 spot size of the order of 0.05 mm to 0.50 mm.

12

The system of any of claims 15 to 29, in which 13 34. there are multiple light sources and means are 14 provided for time multiplexing the multiple 15 sources such that: each source is switched on and 16 generates an optical pulse, or a set of optical 17 pulses, the pulse, or set of pulses, generates an 18 acoustic signal that is detected by the detector, 19 20 and each source is pulsed in sequence until all 21 sources have been used to generate their own 22 signals.

23

24 35. The measuring system of any of claims 15 to 34, in 25 the form of a self contained system including a 26 power supply and a readout, which may be carried 27 on the person and used at any convenient time.

28

29 36. The system of claim 35, including facilities for 30 connection to a cellular telephone, two-way pager 31 or other communication device for routine 32 transmission of measurements taken to a central 33 data collection point.

34

35 37. The system of any of claims 15 to 36, further including means for manipulating the body part

under measurement and for performing additional
measurement of the tissue to obtain other
information about the state of the physiology of
the issue.

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38. The system of claim 37, in which said manipulating means includes means for squeezing a body part, such as an earlobe, and means for making photo acoustic measurements at several different pressures.

10 11

12 39. The system of claim 37 or claim 36, including
13 temperature measurement means for measuring the
14 temperature of the body site, and in which the
15 signal processing means is arranged to apply a
16 correction to the measurements based upon the
17 temperature of the body site.

18 19

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40. The system of claim 39, further including means for inducing temperatures above and below ambient in the body part.

21 22

23 41. The system of any of claims 15 to 40, comprising a
24 means for storing one or both of calibration
25 coefficients and operational parameters in order
26 to calibrate the instrument and to set critical
27 operational parameters.

28

29 42. The system of claim 41, in which the signal 30 processing means is operable to adjust the 31 calibration coefficients and operational 32 parameters to be specific to a particular person.

33

34 43. The system of claim 42, when dependent upon claim 35 14, in which the calibration coefficients and 36 operational parameters specific to a particular

1		person are contained in a storage site located in
2		the removable insert.
3		
4	44.	The system of claim 43, in which additionally
5		calibration coefficients and operational
6		parameters specific to the reader system are
7		stored in the non-removable housing.
8		
9	45.	The measuring system of any of claims 15 to 44,
10		further including connection means for connecting
11		the measuring system to an invasive measuring
12		system for the purpose of calibrating or adjusting
13		the operational parameters of the non-invasive
14		measuring system.
15		
16	46.	The system of claim 45, in which the connection
17		means is selected from a cable link, IR link or
18		radio waves.
19		
20	47.	A method of operating a measurement system as
21		claimed in claim 34 to remove instrument drift
22		from the measurement, the method comprising the
23		steps of:
24		•
25		1) placing a calibration standard in the reader
26		in place of the body part;
27		• • •
28		2) measuring the signal from the standard for
29		each wavelength and storing the values in the
30		calibration storage location;
31		
32		<ol> <li>before making a measurement of a body part,</li> </ol>
33		placing the calibration standard in the
34		reader;
35		

4) measuring the signal from the standard for

1		each source;
1		each source,
2 3		5) comparing the just measured standard values
<i>3</i>		to the stored calibration values;
5		to the stoled calibration variety
6		6) calculating correction factors for each
7		source wavelength.
8		Source wavelength.
9		7) removing the standard and placing the body
10		part in the reader;
11		pure in the reduct,
12		8) measuring the signal from the body part for
13		each source; and
14		caen source, and
15		9) adjusting the measured values using the
16		calculated correction factors.
17		
18	48.	The method of claim 47, in which a further
19		correction factor is calculated for the instrument
20		temperature.
21		-
22	49	A method of measuring a biological parameter in a
23		subject, the method comprising the steps of:
24		
25		directing one or more pulses of optical
26		energy from the exterior into the tissue of a
27		subject along a beam axis, the optical energy
28		having a wavelength selected to be absorbed
29		by tissue components of interest, thereby to
30		produce a photoacoustic interaction;
31		
32		detecting acoustic energy resulting from said
33		photoacoustic reaction by means of a
34		transducer positioned to intercept acoustic
35		energy propagating in a direction other than
36		the forward direction of said beam axis; and

1		deriving from said detected acoustic energy a
2		measure of the parameter of interest.
3		mediate of the parameter of investor
4	50	The method of claim 49, in which the parameter of
5	50	interest is blood glucose, and the optical energy
6		has a wavelength in the range of approximately 600
7		mm to 10,000 mm and a pulse duration of the order
8		of 5 to 500 ms.
9		or 5 to 500 ms.
	<b>6</b> 1	The method of claim 49 or claim 50, in which a
10	51	
11		train of pulses is applied and the detected
12		signals are averaged to derive said measure.
13		
14	52	The method of any of claims 49 to 51, in which
15		said measure is derived from the energy of the
16		detected signal.
17		
18	53	The method of any of claims 49 to 52, in which the
19		optical energy is directed into a body part which
20		is substantially composed of soft tissue and free
21		of bone.
22		
23	54	Apparatus for measuring a biological parameter in
24		a subject, the apparatus comprising:
25		
26		means for directing one or more pulses of optical
27		energy from the exterior into the tissue of a
28		subject along a beam axis, the optical energy
29		having a wavelength selected to be absorbed by
30		tissue components of interest, thereby to produce
31		a photoacoustic interaction;
32		
33		transducer means arranged to detect acoustic
34		energy resulting from said photoacoustic reaction
35		by intercepting acoustic energy propagating in a
36		direction other than the forward direction of said

1		beam axis; and
2		
3		means for deriving from said detected acoustic
4		energy a measure of the parameter of interest.
5		
6	55	Apparatus according to claim 54, in which said
7		directing means incudes means for receiving a
8		selected body part such that the optical energy is
9		directed into a portion of the subject's body
10		which is substantially free of bone.
11		
12	56	A method of correcting measurement of an analyte
13		based on a photoacoustic signal obtained from a
14		living being comprising determining the
15		concentration of other constituents in the being
16		which have a significant effect on the
17		photoacoustic signal and tend to vary from
18		individual to individual or over time, and
19		adjusting the measurement to remove the effect of
20		variations in the concentrations of said other
21		constituents.
22		
23	57	The method of claim 56 in which the analyte is
24		glucose.
25		
26	58	The method of claim 57 in which the concentration
27		of haemoglobin is determined and used to adjust
28		the measurement.
29		
30	59	A method of establishing a photoacoustic signal
31		obtained from a living being comprising using the
32		ratio of the acoustic signal obtained to the
33		optical signal which generated the acoustic signal
34		to determine the concentration of an analyte
35		present in said being.

1	60	The method of claim 59 in which the analyte is
2		glucose.
3		
4	61	A method of normalizing a photoacoustic signal
5		obtained from directing an optical beam on the
6		tissue of a living being comprising determining
7		the dependence of the photoacoustic signal on the
8		energy of the optical beam from a series of
9		measurements at different energies for the type of
LO		tissue involved.
l1		
L 2		
1 7		





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Application No: Claims searched:

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1 to 55

Examiner:

**Grant Bedford** 

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## Patents Act 1977 Search Report under Section 17

## Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): GlG (GPB)

Int Cl (Ed.6): G01N (21/17 33/483 33/487 33/49), A61B (5/00 5/14)

Other: Online: WPI INSPEC

## Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
Х	EP 0282234 A1	(DOWLING) See figure 4 and page 8 lines 1 to 3 in particular.	1 and 14 at least
X,E	EP 0829224 A2	(COLUMBUS) See figure 2 in particular.	1 and 14 at least
X,E	EP 0829225 A2	(COLUMBUS) See figure 1 in particular.	1 and 14 at least
х	Medical & Biological Engineering & Computing, Vol. 31(3), pp. 284-290, May 1993		1 and 14 at least
х	Physics in medicine	and biology, Vol. 38(12), pp. 1911-1922, Dec 1993	1 and 14 at least

X Document indicating lack of novelty or inventive step Y Document indicating lack of inventive step if combined

Document indicating lack of inventive step if combined with one or more other documents of same category.

<sup>&</sup>amp; Member of the same patent family

A Document indicating technological background and/or state of the art.

P Document published on or after the declared priority date but before the filing date of this invention.

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